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SOME EFFECTS OF 138 MEV PROTONS ON PRIMATES

The Radiations of Space III

GLENN V. DALRYMPLE, Captain, USAF, MC, et al.

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USAF School of Aerospace Medicine
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas

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(10) GLENN V. DALRYMPLE, Captain, USAF, MC
IAN R. LINDSAY, Wing Commander, RAF
JOHN J. GHIDONI, Captain, USAF, MC
JOHN C. MITCHELL B.S.
HAROLD L. KUNDEL, Captain, USAF, MC

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FOREWORD

This report was prepared in the Radiobiology Branch under task No. 775704. The paper was submitted for publication on 1 July 1965. The work was accomplished between January and April 1965.

The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

The authors wish to express their appreciation for the cooperation and interest shown by the staff of the University of Harvard Synchrocyclotron facility; without their assistance this study could not have been completed. Also, Dr. A. Koehler, of the cyclotron staff, contributed many valuable discussions.

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Harold V. Ellingson

HAROLD V. ELLINGSON
Colonel, USAF, MC
Commander

ABSTRACT

One hundred two primates *(Macaca mulatta)* were irradiated with spaced doses of 138 Mev protons ranging from 105 to 1,220 rads. An $LD_{50/30}$ of 516 ± 30 rads was estimated from the cumulative mortality data. A comparison of the proton $LD_{50/30}$ with the $LD_{50/30}$ from a previous study in which primates were irradiated with 2 Mev x-rays provides an estimate of 1.30 ± .09 (S.E.) for the mortality RBE. Adjusting the 2 Mev x-ray $LD_{50/30}$ to correspond to the 138 Mev proton dose rate gives an RBE of 1.04. Changes in total leukocyte count, lymphocyte count, neutrophil count, platelet count, hemoglobin concentration, hematocrits, LDH concentrations, and SGOT concentrations indicate an RBE of 1 for 138 Mev protons as compared to 2 Mev x-rays. The only findings which were significantly different between these qualities of radiation were clinical. Considerably more pronounced signs of gastrointestinal injury and hemorrhage were produced by 138 Mev protons as compared to equivalent doses of 2 Mev x-rays.

SOME EFFECTS OF 138 MEV PROTONS ON PRIMATES

The Radiations of Space III

I. INTRODUCTION

Data from balloon and satellite flights of the past 10 years indicate that high energy protons will represent the most significant radiation hazard to man when he penetrates deep space (1). While a large fraction of these protons will be absorbed by the walls of a space vehicle, many will be able to penetrate even the thickest shielding and gain entry into the interior. As the space voyages increase in length, proportionately larger doses will be absorbed by the occupants.

The planning for these future space voyages certainly requires an understanding of the biologic effects produced by protons. Unfortunately, the amount of available information is small. The experiments described in this communication represent part of a large study designed to determine the biologic effectiveness of protons, such as occur in space.

The 138 Mev proton energy is a desirable energy for performing experiments with the small primates which have been used for this as well as prior studies. The protons of this energy have sufficient range in tissue to provide a homogeneous dose distribution throughout the volume of the animal. These protons have a linear energy transfer (LET) similar to the 2 Mev x-rays previously used to irradiate primates (2).

II. EXPERIMENTAL METHODS AND MATERIALS

One hundred two small primates *(Macaca mulatta)* were used. They had a mean weight of 3.8 ± .4 (S.D.) kg., and the weights ranged from 3.1 to 4.9 kg. There were 57 males and 45 females. The details of the animal care practiced at the USAF School of Aerospace Medicine have already been described (2).

The animals were divided into two groups (group I and group II) of 83 and 19 animals, respectively, and were given single spaced doses of 138 Mev protons (table I). The monkeys of group I were divided into subgroups, A and B. Those in subgroup A were bled by femoral venipuncture prior to irradiation and on days 1, 2, 4, 7, 15, 30. 60, and 90 after exposure, for hematologic studies and serum enzyme assays. Total leukocyte counts, leukocyte differentials, platelets, hemoglobin concentrations, microhematocrits, serum lactic dehydrogenase (LDH) concentrations, and serum glutamic oxalacetic transaminase (SGOT) concentrations were measured. The methods used for the collection and handling of the samples, the hematologic studies, and the serum enzyme assays have been previously described (2). The animals in subgroup B were irradiated but not bled.

At least 1 month prior to irradiation, baseline Fe^{59} ferrokinetics were performed on the animals of group II (3). Plasma disappearance half-times and 8- and 10-day RBC uptakes were measured. At 48 hours postirradiation, the Fe^{59} studies were repeated.

During the initial 30 days postirradiation, the animals were observed hourly for clinical changes and mortality. These observations were continued at approximately 8-hour intervals during the 30- to 90-day period.

All dead animals were necropsied according to methods already documented (2).

TABLE I

Cumulative mortality after 138 Mev proton irradiation

Dose (rads)	Study	Number of animals	Number dead at 30 days (all groups)	Percent dead at 30 days	Mean survival time of nonsurvivors (days)
1,220	I. a. Bled*	—	—	—	—
	b. Nonbled	5	5	100	8.8
1,080	I. a. Bled	3	12	100	8.4
	b. Nonbled	6	—	—	—
	II. †	3	—	—	—
930	I. a. Bled	4	14	100	10.4
	b. Nonbled	7	—	—	—
	II.	3	—	—	—
780	I. a. Bled	4	11	85	12.4
	b. Nonbled	7	—	—	—
	II.	2	—	—	—
650	I. a. Bled	3	11	85	13.7
	b. Nonbled	7	—	—	—
	II.	3	—	—	—
500	I. a. Bled	4	5	38	17.0
	b. Nonbled	7	—	—	—
	II.	2	—	—	—
360	I. a. Bled	4	2	15	20.0
	b. Nonbled	7	—	—	—
	II.	3	—	—	—
210	I. a. Bled	4	1	10	23.0
	b. Nonbled	3	—	—	—
	II.	3	—	—	—
105	I. a. Bled	3	0	0	—
	b. Nonbled	1	—	—	—
0	I. a. Bled	4	0	0	—

*Bled for hematologic studies and serum enzyme assays.

†Fe^{59} ferrokinetics.

Protons

The Harvard University Synchrocyclotron was used as a source of protons. Figure 1 is a diagram of the exposure arrangement. The 160 Mev protons from the cyclotron drift pipe were incident on a 7.6 gm./cm.^{2} lead scatterer which defocused the beam and attenuated the proton energy to 138 Mev. At 360 cm. from the scatterer, the proton beam had an approximate gaussian intensity profile with a full width at half maximum of 41 cm., which was centered about the original beam axis.

The primates were exposed at 360 cm. from the scatterer while contained in a cylindric hardware cloth cage of either 15.2 cm. or 17.8 cm. diameter and 38.1 cm. inside height. To

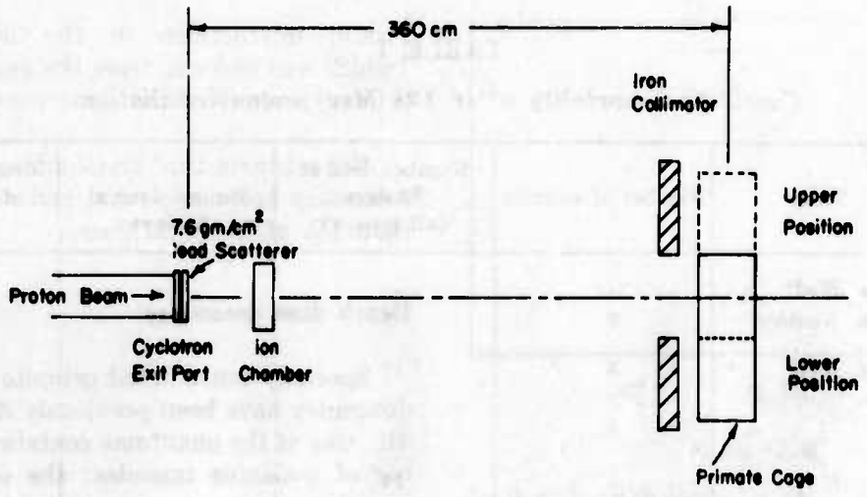

FIGURE 1

Diagram of the exposed arrangement. The dotted line represents the upper position occupied by the exposure cage.

obtain a uniform dose over the primate, the beam was collimated vertically to 20.3 cm. The primate was exposed in two portions by a 20.3-cm. vertical displacement of the cage midway through the exposure. The beam was shut down during the motion of the cage. During irradiation the cage was rotated at 2 r.p.m. about the vertical axis to improve the depth dose distribution. The beam uniformity and energy were measured by polyethylene foil activations (4).

The proton field provided by this combined exposure technic was homogeneous. With the exception of a 1-cm. region of overlap of the fields, as a result of the changing of the two cage positions, the dose along the axis of the cage varied less than 12% at the peripheral extremes as compared with the center line. This dose distribution meets the criteria for homogeneity described in HBS Handbook 88 (5). At the narrow strip of overlap of the fields (less than 9 mm. wide), the dose was approximately 60% higher than at an adjacent point outside the region of overlap. Since the monkey was able to move somewhat during irradiation, the point of buildup was flattened. Therefore, we estimate that an average of approximately 30% buildup of dose occurred over a 1-cm. strip located at the level of the midportion of the cage. Since the monkey was in a sitting position during exposure, the anatomic region of this buildup of dose was in the lower one-third of the thorax. A small portion of the upper arms was also included.

All exposures were monitored by an ion chamber (fig. 1) (4), which had been previously calibrated with a Faraday cup placed at the 360-cm. exposure position. The doses were calculated on the basis of 1.145×10^{-7} rads/proton/cm.^{2} Although the ion chamber allowed accurate ($\pm 5\%$) measurements of the total doses, the dose rates varied somewhat. That portion of the animal directly under the beam was irradiated with dose rates ranging between 100 and 130 rads/min. Since the animal was irradiated in two portions (upper and lower), the dose rate averaged over the total time of exposure was 50 to 65 rads/min. For purposes of discussion, we assume that a nominal dose rate of 57 rads/min. was used.

The contamination of the scattered beam by secondary protons from the lead scatterer was measured by the Harvard cyclotron personnel to be less than 4% of the total dose. A calculation based on data by Bertini and Dresner

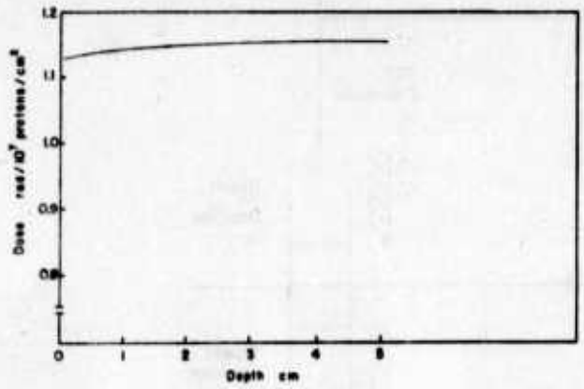

FIGURE 2

Graphical plot of the calculated depth dose distribution in a rotated unit-density cylinder of 5-cm. radius. Notice that the distribution is essentially flat from the surface to the 5-cm. depth.

(6, 7), however, indicates much less than 1% contamination at 360 cm. from the scatterer. The neutron dose was measured with a Bonner sphere to be approximately 0.003 rads/min. off axis near the primate exposure position. The γ-ray dose rate, as measured with a Victoreen R meter, was approximately 0.1 rads/min. Proton interactions in the iron collimator (which was 30.5 cm. from the animal) were the primary sources of the γ-ray contaminations.

We estimate that the contamination due to secondary protons, γ-rays, and neutrons is less than 1% of the total dose.

Depth dose dosimetry

Specially constructed primate phantoms for dosimetry have been previously described (2, 3, 4). One of the phantoms contains a large number of α-alanine capsules; the other phantom contains glass-rod microdosimeters. Both of these dosimetry systems have been found to be adequate for measuring the depth dose distribution produced by high energy protons (3, 4, 8, 9). The phantoms were irradiated in the same manner as the primates in that they were placed in an exposure cylinder, rotated during irradiation, and irradiated in two portions (upper and lower).

Less than 5% variation in dose rate throughout the volume of the phantoms was

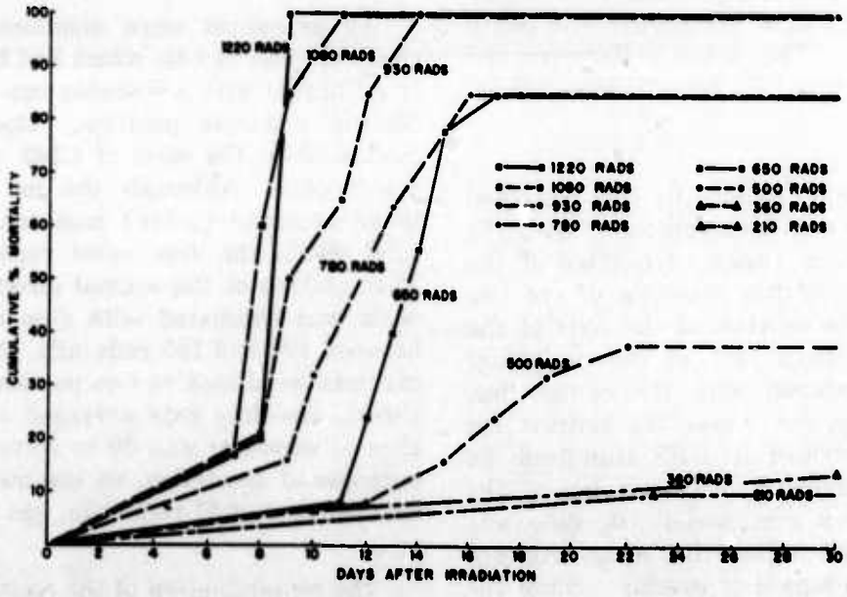

FIGURE 3

Cumulative mortality after irradiation. Since no deaths occurred after 105 rads, this was not plotted.

measured by the alanine and the glass-rod systems. These measurements agree with calculations made with a digital computer (4). Figure 2 shows this calculated dose distribution for the idealized case of a tissue-equivalent cylinder which is 10 cm. in diameter and which is rotating in a homogeneous field of unidirectional 138 Mev protons normal to the cylinder axis. The energy deposition values were taken from published data (10). Therefore, the irradiated primates were considered to have received homogeneous, total-body exposures (5).

III. RESULTS

Table I and figures 3 and 4 summarize the mortality after irradiation. Also plotted on figure 4 are data from a previous study in which primates were irradiated with 2 Mev x-rays (2).

An $LD_{50/30}$ of 516 ± 31 (S.E.) rads for the 138 Mev protons was estimated by probit analysis from the 30-day mortality data (11). The equation for the regression is:

$$Y = 5.2416 + 7.6156\ (X-2.7447)$$

where Y is in probits and X in $\log_{10}$ of the doses. The chi-square for the regression is 1.735 (3 d.f.), which is not significant and which indicates no departure from linearity. The slope standard error is 1.4829.

The postirradiation total white cell counts, neutrophil counts, lymphocyte counts, platelet counts, and hemoglobin and hematocrit levels are summarized in tables II-VI, respectively. Part of these results are plotted on figures 5-9; only in this instance, the results are normalized to percent of preirradiation baseline. On the same figures, similarly normalized data from the 2 Mev x-ray studies are included for comparison (2).

The changes in the hematologic measurements are similar for the animals irradiated with equivalent doses of either 138 Mev protons or 2 Mev x-rays. In both cases, a prompt drop in lymphocytes with an associated rise in neutrophils occurred on the 1st postirradiation

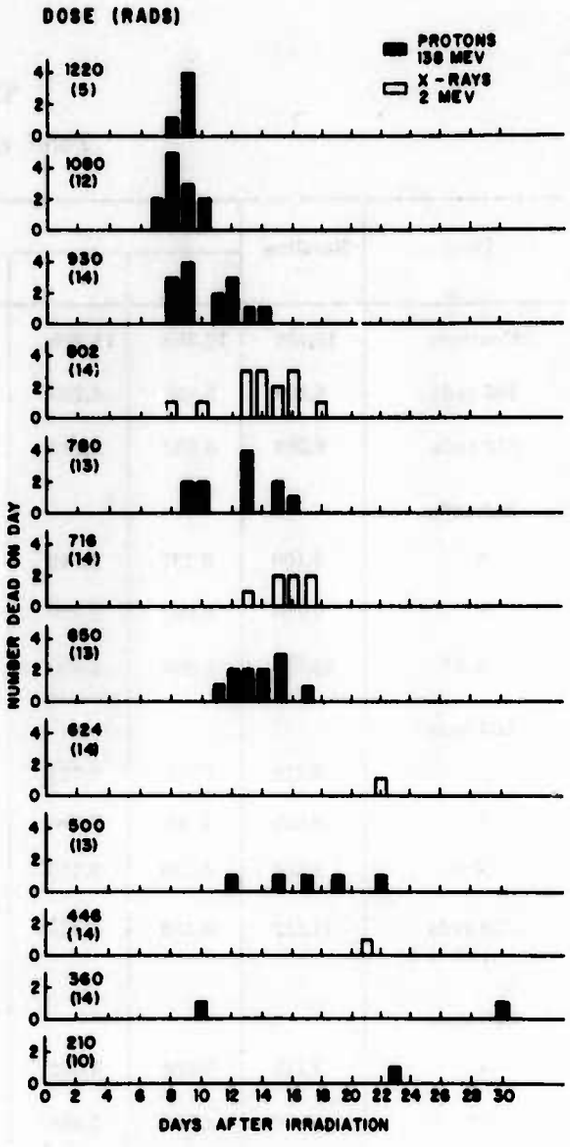

FIGURE 4

Daily mortality after irradiation with 138 Mev protons and 2 Mev x-rays. Notice that relatively more deaths occurred before the 12th postirradiation day after 138 Mev protons as compared with 2 Mev x-rays.

day. This was followed by a progressive decrease in the levels of the total white cell counts, as well as the neutrophil and lymphocyte components, through the 15th postirradiation day. The degree of depression of the measurements was similar for both qualities of radiation. While the rate of decrease of the total white cell counts tended to be more rapid

TABLE II

Total white cell count

Dose	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	11,466	12,300	11,900	9,950	12,000	11,616	15,967	11,383	12,133
105 rads	8,330	5,050	4,266	2,650	2,866	4,725	3,700	6,700	5,900
210 rads	9,500	6,500	3,288	3,025	2,463	2,200	4,225	5,325	7,338
360 rads									
A	9,100	6,737	2,712	2,238	1,066	1,150	4,750	4,625	7,000
S	7,950	6,683	2,817	2,600	1,400	1,150	4,750	4,625	7,000
N-S*	12,550	6,900	2,400	1,150	400	—	—	—	—
500 rads									
A	9,712	6,700	2,725	2,450	937	1,200	4,250	7,200	8,910
S	9,925	7,700	3,300	3,300	1,325	1,825	4,250	7,200	8,910
N-S	9,500	5,700	2,150	1,600	550	575	—	—	—
650 rads (all N-S)	11,112	8,433	3,733	2,050	480	400	—	—	—
780 rads									
A	9,175	7,225	3,262	2,038	775	1,300	7,750*	17,600*	9,950*
S*	10,400	8,550	3,200	650	1,950	2,050	7,750	17,600	9,950
N-S	8,767	6,783	3,283	2,500	383	550*	—	—	—
930 rads (all N-S)	9,900	6,750	2,700	1,390	1,900	—	—	—	—
1,080 rads (all N-S)	8,300	5,133	2,283	783	—	—	—	—	—

The entries in the table are the average counts, per cubic millimeter, of the bled animals (except the survivor and nonsurvivor subdivisions of the 360-rad, 500-rad, and 780-rad groups).

A = All animals; S = Survivors; N-S = Nonsurvivors.

*One animal.

TABLE III

Neutrophils (per total WBC)

Dose	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	3,540	3,136	3,333	4,212	5,173	3,943	4,075	3,207	2,587
105 rads	2,200	3,112	2,591	1,630	851	2,937	1,033	2,009	1,170
210 rads	1,502	5,256	2,066	2,245	1,416	776	533	1,088	1,852
360 rads									
A	1,425	5,357	1,591	1,577	639	305	1,060	1,358	1,816
S	1,565	5,349	1,489	1,946	903	305	1,060	1,358	1,816
N-S*	1,004	5,382	1,896	460	112	—	—	—	—
500 rads									
A	3,010	5,760	1,650	1,871	345	290	734	2,170	2,867
S	2,504	6,385	2,080	2,684	510	581	734	2,170	2,867
N-S	3,517	5,136	1,221	1,059	182	0	—	—	—
650 rads (all N-S)	2,647	6,942	2,796	1,675	167	0	—	—	—
780 rads									
A	1,120	3,763	2,642	1,556	171	605	4,883*	6,512*	3,316*
S*	936	8,123	2,752	117	390	1,210	4,883	6,512	3,316
N-S	1,180	6,310	2,605	2,036	98	0*	—	—	—
930 rads (all N-S)	2,377	5,360	2,254	1,120	1,349	—	—	—	—
1,080 rads (all N-S)	1,569	4,726	1,613	460	0*	—	—	—	—

*One animal.

TABLE IV

Lymphocytes

Dose	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	7,705	8,540	8,020	5,676	6,650	7,412	10,953	7,864	9,229
105 rads	5,961	1,850	1,342	983	1,952	1,755	2,418	4,545	4,535
210 rads	7,730	1,220	1,109	765	1,032	1,402	3,549	3,962	4,751
360 rads									
A	7,549	1,279	992	645	416	760	3,593	3,116	5,082
S	6,300	1,292	1,162	630	480	760	3,593	3,116	5,082
N-S*	11,295	1,242	480	690	288	—	—	—	—
500 rads									
A	6,549	906	732	560	592	837	3,335	4,742	5,908
S	7,228	1,278	977	579	816	1,171	3,335	4,742	5,908
N-S	5,870	535	487	541	369	575	—	—	—
650 rads (all N-S)	8,157	1,295	870	375	316	400	—	—	—
780 rads									
A	7,680	419	541	466	601	592	2,403*	10,032*	6,632*
S*	8,736	256	448	520	1,560	635	2,403	10,032	6,632
N-S	7,380	474	572	447	281	550*	—	—	—
930 rads (all N-S)	7,400	1,122	423	265	550	—	—	—	—
1,080 rads (all N-S)	6,333	383	606	314	100*	—	—	—	—

The entries in the table are the average counts, per millimeter, of the bled animals (except the survivor and nonsurvivor subdivisions of the 360-rad, 500-rad, and 780-rad groups).

A = All animals; S = Survivors; N-S = Nonsurvivors.

*One animal.

TABLE V

Platelets

Dose	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	370	461	361	282	302	435	369	301	366
105 rads	385	379	372	275	412	156	295	353	340
210 rads	339	352	388	284	360	112	271	288	285
360 rads									
A	251	351	313	257	249	154	265	295	224
S	253	377	326	287	339	154	265	295	224
N-S*	243	273	272	169	71	—	—	—	—
500 rads									
A	294	328	349	281	233	47	269	343	285
S	286	347	335	281	261	61	269	342	285
N-S	301	310	363	281	206	32	—	—	--
650 rads (all N-S)	387	327	401	280	239	33	—	—	—
780 rads									
A	368	345	319	298	127	51	309*	444*	223*
S*	441	442	408	340	31	86	309	444	223
N-S	343	313	289	285	159	16*	—	—	—
930 rads (all N-S)	387	367	420	323	203	—	—	—	—
1,080 rads (all N-S)	270	265	282	168	146	—	—	—	—

The entries in the table are the average counts ($\times 10^3$/mm.^{3}) of the bled animals (except the survivor and the nonsurvivor subdivisions of the 360-rad, 500-rad, and 780-rad groups).

A = All animals; S = Survivors; N-S = Nonsurvivors.

*One animal.

TABLE VI

Hemoglobin (gm./100 ml. blood) and hematocrit (%)

Dose	Baseline		Days after irradiation													
			1		2		4		7		15		30		60		90	
	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT	Hb	HCT
Controls	13.4	43	12.9	41	12.8	39	12.0	38	11.8	38	11.4	36	12.6	40	12.7	40	13.2	42
105 rads	12.7	40	13.5	43	12.2	38	11.7	37	11.0	33	11.0	35	13.5	40	12.9	41	13.0	41
210 rads	11.8	38	13.0	41	12.2	38	10.2	34	9.6	30	10.8	34	10.9	34	12.1	39	12.7	40
360 rads																		
A	11.4	36	13.0	41	11.9	38	10.7	36	10.6	34	9.5	30	10.9	33	12.0	38	11.6	38
S	11.1	34	13.1	41	12.0	38	10.3	35	9.9	33	9.5	30	10.9	33	12.0	38	11.6	38
N-S*	12.3	39	12.8	40	11.7	36	12.1	40	12.2	38	—	—	—	—	—	—	—	—
500 rads																		
A	11.6	36	12.1	38	11.2	35	10.8	35	10.5	33	7.1	22	10.5	32	11.4	37	12.7	41
S	11.6	36	12.2	38	11.1	35	9.9	33	10.4	32	8.4	27	10.5	32	11.4	37	12.7	41
N-S	11.6	36	12.0	38	11.3	35	11.6	38	10.6	34	5.7	18	—	—	—	—	—	—
650 rads (all N-S)	11.4	36	12.5	40	12.1	38	10.7	36	11.3	36	5.0	15	—	—	—	—	—	—
780 rads																		
A	12.5	39	12.9	41	11.8	37	11.2	37	11.7	37	7.4	22	11.4*	36*	13.5*	42*	12.1*	38*
S*	12.4	39	13.7	44	11.0	36	10.7	35	12.0	39	10.5	33	11.4	36	13.5	42	12.1	38
N-S	12.5	39	12.7	39	12.1	37	11.3	37	11.6	36	4.2*	12*	—	—	—	—	—	—
930 rads (all N-S)	12.0	38	11.6	37	10.8	34	10.6	35	11.2	36	—	—	—	—	—	—	—	—
1,080 rads (all N-S)	12.0	40	11.7	37	11.6	37	10.1	34	12.8*	41*	—	—	—	—	—	—	—	—

The entries in the table are the average measurements of the bled animals (except the survivor and nonsurvivor subdivisions of the 360-rad, 500-rad, and 780-rad groups).

A = All animals; S = Survivors; N-S = Nonsurvivors.

*One anim .

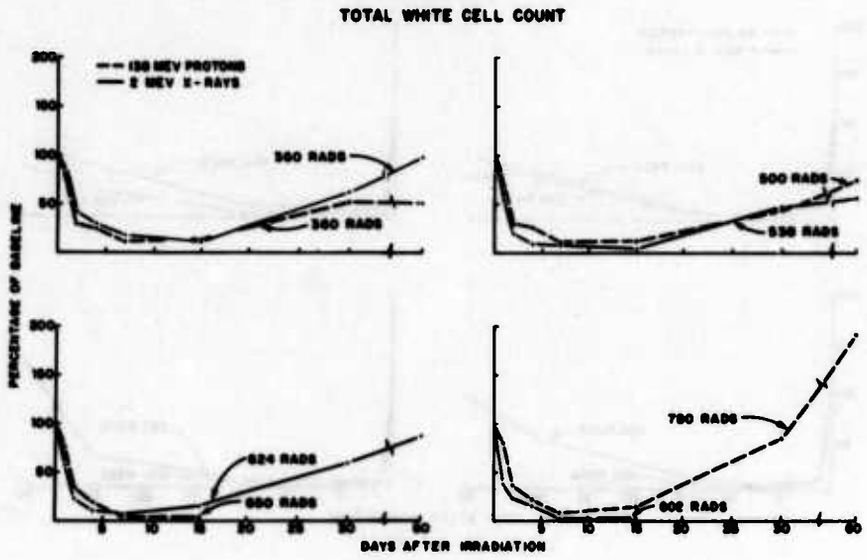

FIGURE 5

Total white cell counts after irradiation with 138 Mev protons and 2 Mev x-rays. There were no survivors past 15 days after 650 rads of 138 Mev protons and 802 rads of 2 Mev x-rays. The single animal which survived 780 rads of 138 Mev protons had an elevated white count at 6 days postirradiation, which was caused by a severe salmonella enteritis. This cleared spontaneously and the counts returned to normal by 90 days.

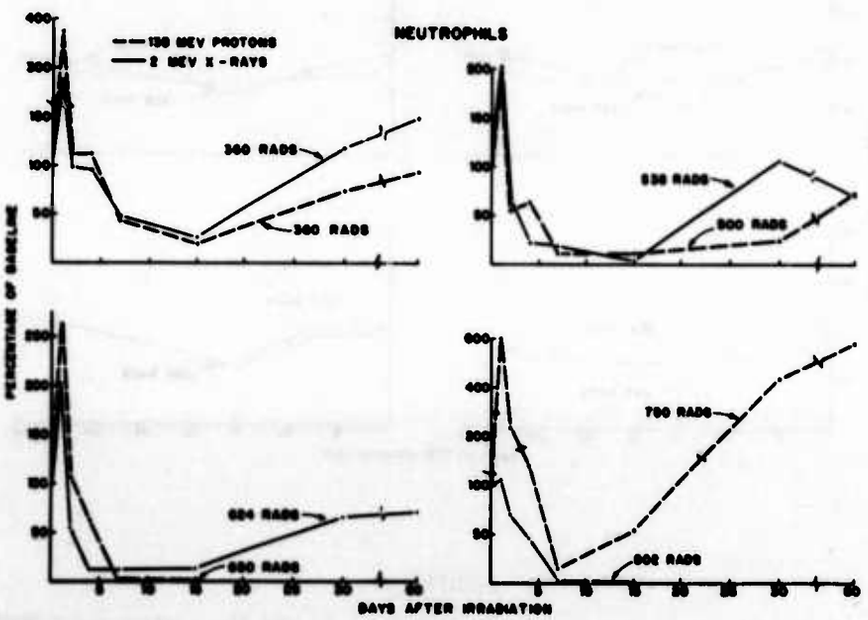

FIGURE 6

Neutrophil counts after irradiation with 138 Mev protons and 2 Mev x-rays.

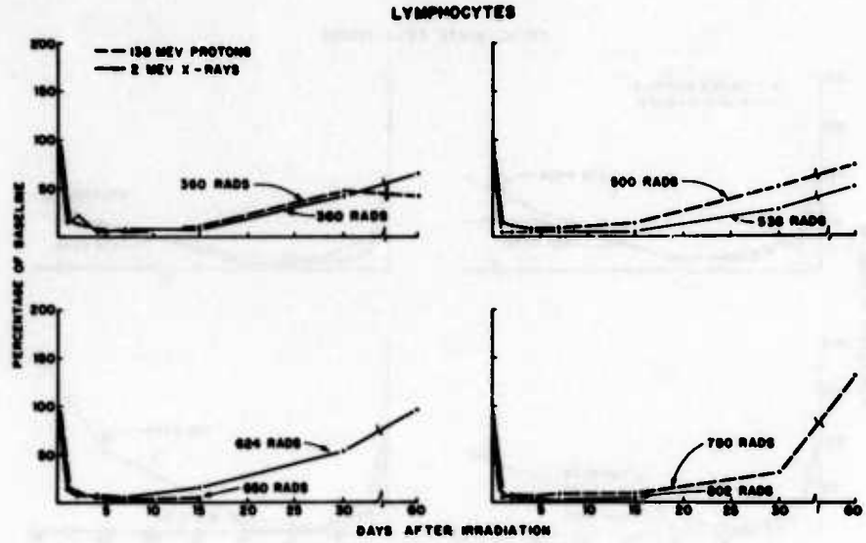

FIGURE 7

Lymphocyte counts after irradiation with 138 Mev protons and 2 Mev x-rays.

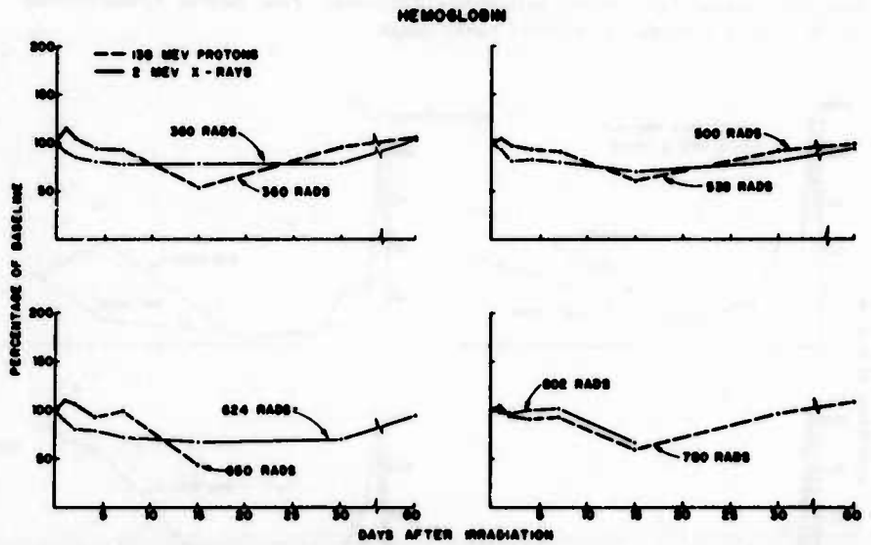

FIGURE 8

Hemoglobin concentrations after irradiation with 138 Mev protons and 2 Mev x-rays.

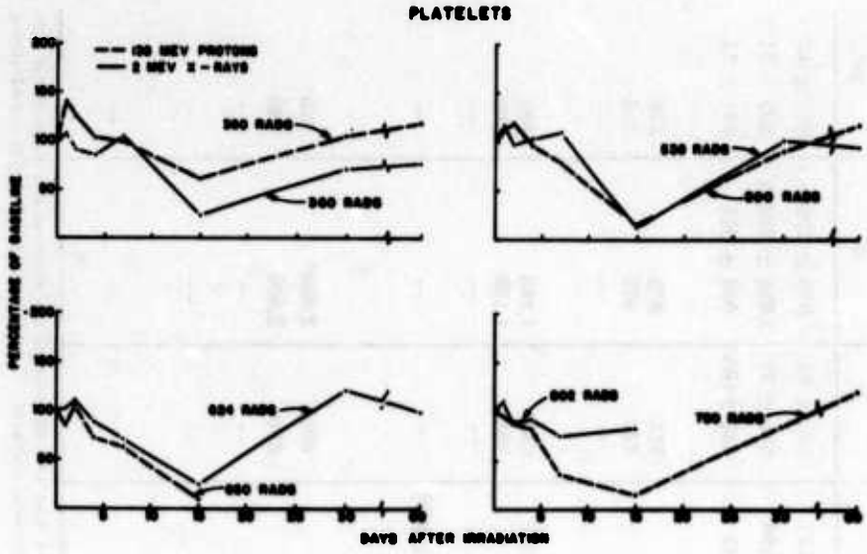

FIGURE 9

Platelet counts after irradiation with 138 Mev protons and 2 Mev x-rays. The somewhat unexpected high platelet count after 802 rads of 2 Mev x-rays occurred in a single animal in terminal status that was severely dehydrated. Our impression is that the dehydration caused hemoconcentration, which produced a platelet count that was excessively high.

after the highest doses, the magnitude of the change was generally not significantly different at the lower dose levels (210 to 360 rads) as compared with the higher doses. The degree of depression of the total leukocyte count was of little or no prognostic value. At 30 days postirradiation normal ranges, which persisted through the 90-day observation period, were reached in the survivors. The elevated 60-day white cell count (which was caused by elevation of both the neutrophil and lymphocyte components) in the animal surviving 780 rads of 138 Mev protons occurred at the height of an episode of salmonella enteritis. Therefore, this elevation is a response to an infectious disease and not a result of changes produced by protons.

The changes in the platelet counts, the hemoglobin concentrations, and the hematocrits after 138 Mev proton irradiation paralleled the changes caused by 2 Mev x-rays. While the platelet counts remained normal through day 7, by day 15 these counts dropped to clinically significant levels. This depression was transitory in the survivors; the counts returned to normal ranges by day 30. The hemoglobin concentrations and the hematocrits dropped slightly during the first 4 postirradiation days, mostly as a result of the rather frequent blood sampling (2). The depression that occurred by day 15, however, exceeded that which could be explained by the venipunctures and must be considered to be a consequence of irradiation. In surviving animals, normal ranges were again reached by day 30.

The postirradiation LDH and SGOT concentrations are given in tables VII and VIII. At all dose levels, significant elevation of the LDH concentrations occurred during the first 7 postirradiation days; Student's t-test was used for comparison of group means. By day 15, however, the concentrations resumed the normal range. The somewhat large mean value that occurred on day 15 after 650 rads of 138 Mev protons is the result of a single animal in terminal status, which had an LDH level of 2,760 units/ml. serum. Our experience has been that the highest levels of both LDH and SGOT are found in animals that are *in extremis* (2, 3).

TABLE VII

Lactic dehydrogenase (LDH)

Dose	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	516 ± 88†	760 ± 150†	714 ± 103‡	716 ± 162‡	410 ± 80	466 ± 157	572 ± 83	885 ± 292§	291 ± 46
105 rads	449 ± 130	416 ± 88	612 ± 200	999 ± 101§‖	917 ± 37§‖	347 ± 100	585 ± 93	1,038 ± 364‡§	299 ± 41
210 rads	586 ± 195	1,002 ± 252§	840 ± 281§	994 ± 290§	834 ± 249§	343 ± 42	646 ±106	984 ± 92§	381 ± 41
360 rads									
A	472 ± 73	2,691 ± 2,810§	1,382 ± 665§	1,122 ± 825§	998 ± 410§	297	723	875	376
S	459 ± 81	3,265 ± 3,035	1,544 ± 696	1,284 ± 899	840	297	723	875	376
N-S*	510	970	893	633	316	—	—	—	—
500 rads									
A	593 ± 93	966 ± 204§	1,025 ± 425§	1,108 ± 364§	1,008 ± 334§	338 ± 32	783	1,188	698
S	653	1,043	870	1,351	1,122	350	783	1,188	698
N-S	533	890	1,180	865	895	326	—	—	—
650 rads (all N-S)	633 ± 27	960 ± 119‡§	1,602 ± 610§	971 ± 238§	574 ± 133	1,398 ± 1,200§	—	—	—
780 rads									
A	692 ± 381‡	1,287 ± 349§	1,594 ± 630§	1,371 ± 374§	611 ± 222	564	690*	2,600*	440*
S*	1,283	1,683	1,566	1,806	510	553	690	2,600	440
N-S	494 ± 197	1,155 ± 302	1,603 ± 728	1,226 ± 321	644 ± 214	575*	—	—	—
930 rads (all N-S)	446 ± 88	965 ± 190‡§	1,190 ± 270§‖	908 ± 174‡§	398 ± 44	—	—	—	—
1,080 rads (all N-S)	523 ± 40	1,063 ± 228‡§	1,255 ± 144§‖	945 ± 165‡§	680	—	—	—	—

The entries in the table are the means and standard deviations, in units per milliliter of serum, of the measurements of 4 bled animals (except the survivor and nonsurvivor subdivisions of the 360-rad, 500-rad, and 780-rad groups). Where no standard deviation is listed, fewer than three measurements were available. Normal range based on 124 examinations, 460 ± 159 units.

A = All animals; S = Survivors; N-S = Nonsurvivors.

*One animal.

†Standard deviation.

‡$P < .01$ compared with pre-established normal range.

§$P < .001$ compared with pre-established normal range.

‖$P < .001$ compared with preirradiation baseline.

TABLE VIII

Glutamic oxalacetic transaminase (SGOT)

Dose	Baseline	Days after irradiation							
		1	2	4	7	15	30	60	90
Controls	25 ± 11†	26 ± 2	28 ± 5	27 ± 5	27 ± 1	17 ± 1	24 ± 6	31 ± 7	18 ± 3
105 rads	26 ± 8	23 ± 2	39 ± 11§	34 ± 3	29 ± 5	29 ± 5	23 ± 2	33 ± 7	18 ± 2
210 rads	35 ± 5‡	56 ± 36§	46 ± 27§	45 ± 25§	32 ± 10	35 ± 6‡	27 ± 16	37 ± 5‡	19 ± 3
360 rads									
A	28 ± 7	363 ± 545	132 ± 156§	57 ± 50§	25 ± 14	32	22	32	23
S	29 ± 8	473 ± 592	169 ± 164	70 ± 53	33	32	22	32	23
N-S*	26	35	21	20	10	—	—	—	—
500 rads									
A	28 ± 3	72 ± 39§	39 ± 9§	39 ± 24‡	33 ± 8	35 ± 18	28	41	37
S	25	61	33	54	36	49	28	41	37
N-S	30	82	45	24	30	21	—	—	—
650 rads (all N-S)	31 ± 1	37 ± 3‡	50 ± 12§‖	49 ± 33§	20 ± 2	119 ± 89§	—	—	—
780 rads									
A	32 ± 8‡	99 ± 52§‖	64 ± 26§	42 ± 5‡‖	24 ± 7	70	32*	68*	34*
S*	43	135	90	41	17	53	32	68	34
N-S	28 ± 4	87 ± 55	55 ± 24	43 ± 6	26 ± 7	87*	—	—	—
930 rads (all N-S)	26 ± 6	75 ± 61§	76 ± 37§‖	35 ± 17	18 ± 4	—	—	—	—
1,080 rads (all N-S)	33 ± 5	67 ± 18§	59 ± 26§	29 ± 10	24	—	—	—	—

The entries in the table are the means and standard deviations, in units per milliliter of serum, of the measurements of the bled animals (except for the survivor and nonsurvivor subdivisions of the 360-rad, 500-rad, and 780-rad groups). Where no standard deviation is listed, fewer than three measurements were available. Normal range based on 202 examinations, 26 ± 7 units.

A = All animals; S = Survivors; N-S = Nonsurvivors.

*One animal.

†Standard deviation.

‡$P < .01$ compared with pre-established normal range.

§$P < .001$ compared with pre-established normal range.

‖$P < .01$ compared with preirradiation baseline.

The LDH results were normalized to percent of preirradiation baseline and plotted (fig. 10) along with comparable data from the 2 Mev x-ray study (2). Parallel elevations of the LDH levels after 138 Mev protons and 2 Mev x-rays occurred through day 7, after which they returned to the normal range. The elevation at 60 days after 780 rads of the protons occurred in conjunction with the salmonella enteritis previously described.

Significant elevation of SGOT levels above preirradiation baseline and above the pre-established normal range was found during the initial 15 days after doses greater than 500 rads of 138 Mev protons. Increased SGOT levels

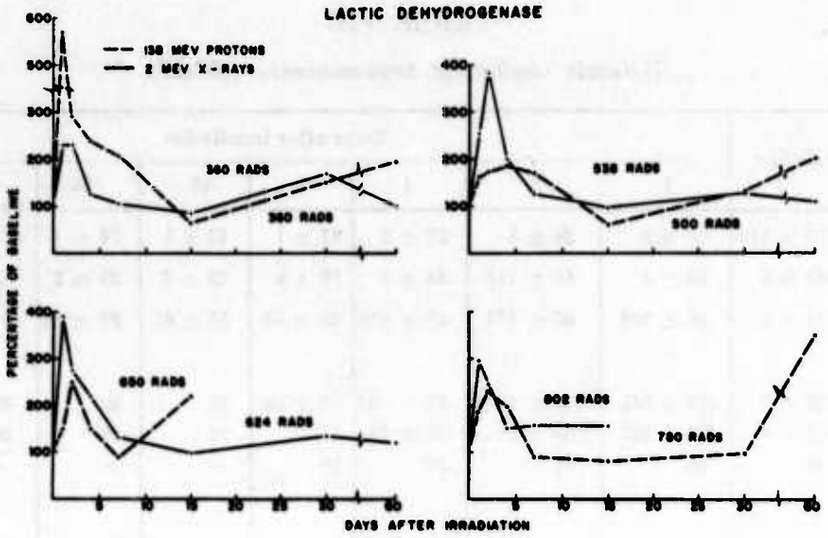

FIGURE 10

Lactic dehydrogenase (LDH) concentrations after irradiation with 138 Mev protons and 2 Mev x-rays. As was the case with the blood counts, the LDH level increased at 60 days postirradiation in the animal that had the salmonella enteritis.

occurred sporadically during the first 4 post-irradiation days in the group of monkeys that received 360 rads. These elevations followed such an erratic time course that the group means do not completely reflect the magnitude of the changes occurring in a given animal.

As was the case after irradiation with 32 Mev protons, a great deal of biologic variability influenced the time of onset of the elevation of both the LDH and SGOT concentrations, as well as the times at which these levels returned to normal (3). Frequently, this circumstance caused the group responses at a given time period to be highly variable. The somewhat large standard deviations (and the subsequent failure of some of the statistical tests of significance) are a direct result of this skewed distribution of results.

Table IX contains the Fe^{59} ferrokinetics results. Prolonged plasma disappearance half-times and severely depressed 8- and 10-day RBC uptakes, as compared with preirradiation baseline, occurred at all dose levels studied. These postirradiation values are also abnormal as compared to the normal ranges found in our laboratory (plasma disappearance half-times, 40 to 130 minutes; RBC uptake, 70% to 100% of injected dose by 8 or 10 days).

While the lengthening of the postirradiation plasma disappearance half-times is highly significant ($P < .001$) as compared with preirradiation values, the magnitude of the lengthening of the half-times is not significantly different at the lowest dose level (210 rads) as compared with the higher doses. This may be demonstrated as follows. Analysis of variance technics were applied to the data of table IX, and the results of this analysis are given in table X. No significant differences between the plasma disappearance half-times were found either between dose levels or between the animals at a given dose level.

Although the lower doses (210 and 360 rads) produced an unmistakable depression of the RBC uptakes, measurable amounts of the Fe^{59} were found at 8 and 10 days after injection. No uptake of the radioisotope could be measured at 10 days after 500 to 1,080 rads,

TABLE IX

Fe^{59} ferrokinetics after 138 Mev proton irradiation

Plasma disappearance half-time (T 1/2) (minutes)			8-day RBC uptake (percent of injected dose)		10-day RBC uptake (percent of injected dose)	
Dose (rads)	Preirradiation	Postirradiation	Preirradiation	Postirradiation	Preirradiation	Postirradiation
210	70 ± 12	263 ± 62*	99 ± 1	6.3 ± 2	95 ± 6	9.5 ± 3.4
360	75 ± 8	259 ± 25	85 ± 1	1.4 ± 1.2	87 ± 4	2.4 ± 1.2
500	69	223	93	.3 ± .2	93	0
650	48 ± 7	237 ± 8	86 ± 15	.67 ± .6	92 ± 8	0
780	78	265	86	0	89	0
930	62 ± 17	230 ± 28	97 ± 5	†	97 ± 4	†
1,080	79 ± 14	227 ± 26	82 ± 12	†	84 ± 7	†

The entries in the table are the average of the measurements from either 2 or 3 animals at each dose level.

*Standard deviation. Where no standard deviation is listed, fewer than three measurements are available.

†No sample taken.

however. These results indicate that doses as low as 210 rads of 138 Mev protons produce severe depression of bone marrow function, as measured by Fe^{59} (as well as the blood counts).

The clinical findings produced by the 138 Mev protons were very similar to those produced by 2 Mev x-rays and other electromagnetic radiations (12-15). Since the clinical changes in the *Macaca mulatta* following x- and γ-irradiation have been documented in detail on several previous occasions, only the more pertinent findings will be described (3, 12-15).

During the first few postirradiation days, no definite clinical signs were observed except for malaise and depression of appetite. After this initial quiescent period, the animals that had received the highest doses of the protons (780 to 1,220 rads) developed signs indicating severe gastrointestinal injury. On or about the 3d postirradiation day, very severe mucous and bloody diarrhea began. At these high dose levels, the mortality occurring between days 8 and 11 was greater than previously observed after similar size doses of 2 Mev x-rays or Co^{60} γ-radiation (fig. 4) (15). It should be recalled that mortality during this time period is primarily the result of gastrointestinal injury. Therefore, when the clinical courses and the mortality patterns of the animals that received equivalent doses of 2 Mev x-rays and 138 Mev protons are compared, the protons produce more severe gastrointestinal injury.

TABLE X

Analysis of variance-plasma disappearance half-times

Source of variation	d.f.	S. Sq.	M. Sq.	F
Between dose levels	6	5,230	872	0.70*
Variation between animals at given dose level	2	3,823	1,912	1.19*
Remainder	12	17,021	1,418	—
Total	20	26,074		

*Not significant at .05 level.

Those animals surviving the period of gastrointestinal injury and those that received intermediate doses (360 to 650 rads) developed signs of hemorrhagic diathesis on or about the 12th postirradiation day. Again, the clinical findings were similar to those produced by

2 Mev x-rays. The intensity of the changes, however, tended to be more severe. Where minimal dermal petechiae and gingival hemorrhages occurred after 2 Mev x-rays, considerably more severe findings occurred after comparable doses of 138 Mev protons. While hemoptysis, massive epistaxis, and extensive gingival hematomas after proton irradiation were common, none of these signs appeared after 2 Mev x-irradiation.

Although 1 animal that had received 360 rads died on the 30th postirradiation day, in general, acute mortality had ceased by the 23d postirradiation day for both the 2 Mev x-ray and 138 Mev proton-irradiated animals. No delayed mortality through the 90-day observation period occurred.

In prior studies with 2 Mev x-rays, no deaths occurred after 360 rads. In the present instance, however, 2 animals died after 360 rads and 1 died after 210 rads of 138 Mev protons.

This report covers the clinical changes found within the first 90 days postirradiation.

Since a detailed description of the necropsy findings will comprise a separate publication, only a brief summary of these results will be included in this report. The histopathologic changes found after 138 Mev proton irradiation are similar to those found after 2 Mev x-irradiation (2). Those animals dying before the 12th postirradiation day had pronounced changes in the gastrointestinal tract. Widespread destruction of the mucosa with many localized hemorrhages was universally present. Large clots of blood and tarry stools were frequently found in the lumen of the colon. There were also extensive hemorrhages in the walls of the colon in association with areas of necrosis.

The animals dying after the 12th day also had gastrointestinal epithelial damage, but it was somewhat less severe than that found in those animals dying earlier. The bone marrow was aplastic; the only residual elements were occasional reticular cells. Comparison of the tissues of animals receiving equivalent doses of 2 Mev x-rays and 138 Mev protons revealed no significant differences.

IV. DISCUSSION

Perhaps the most direct and simple estimation of the RBE (relative biologic effectiveness) is the ratio of the midlethal doses ($LD_{50/30}$'s in this case) produced by the standard and test radiations. To use this method, however, certain experimental and statistical criteria must be met (11). The doses of the test radiation and the standard radiation must be homogeneously distributed throughout the volume of the experimental subject. Otherwise, the results could be seriously biased by critical organs receiving different doses as a result of an inhomogeneous dose distribution. In the present instance, both the standard radiation (2 Mev x-rays) and the test radiation (138 Mev protons) were homogeneously distributed throughout the bodies of the irradiated primates.

In addition to dosimetric considerations, Finney (11) has shown that to compare two treatments (138 Mev protons and 2 Mev x-rays in this case) by the ratio of their mideffective doses, the probit regression curves must be homogeneous with respect to fitting their respective data and these curves must be parallel. He has derived chi-square tests to determine (1) if the data are adequately fitted by the probit regression curves, and (2) if significant departure from parallelism of the curves exists. By the method described by Finney, the chi-square for departure from parallelism of these regression curves is 2.79 (1 d.f.), which is not significant at the .05 level and indicates no departure from parallelism.

Since the data are adequately represented by their respective regression curves and since the curves are parallel, Finney's criteria are met and a valid estimate of the RBE can be made by determining the ratio of the $LD_{50/30}$'s. The 138 Mev proton to 2 Mev x-ray RBE given by this ratio is $1.30 \pm .09$ (S.E.), the standard error being estimated by Finney's method (11).

An additional experimental factor should be considered with regard to the RBE just given. The biologic effectiveness of electromagnetic

radiations is known to be dose-rate dependent, especially in the lower dose-rate ranges (16, 17). While protons have not as yet been shown to be dose-rate dependent, there have been findings in mouse mortality experiments which suggest that they may be as dose-rate dependent as x- and γ-radiations (18). The 2 Mev x-rays used for the prior study were delivered at 10.7 rads/min., while the 138 Mev protons of the present investigation were given at a nominal 57 rads/min. To make a more valid comparison of the $LD_{50/30's}$, some compensation for the dose-rate difference should be made, if possible.

A mathematical model for estimating the influence of dose rate on the midlethal doses produced by x- and γ-irradiation of mice and rats was derived by Bateman et al. (19). This is given (in the authors' notation) by:

$$ED_{50}(a) = ED_{50}(\infty)\left[1 + \frac{0.95}{\sqrt[3]{a}}\right]$$

where $ED_{50}(a)$ is the midlethal dose produced at the dose rate of a rads/min., and $ED_{50}(\infty)$ is the midlethal dose produced by the same radiation delivered at an infinitely high dose rate.

Using the model to adjust the 2 Mev x-ray $LD_{50/30}$ from a dose rate of 10.7 rads/min. to 57 rads/min., we determined a new value of 536 rads. (For purposes of discussion, we tacitly assume that this model can be applied to the primate data.) This would now give an RBE of 1.04 for both radiations delivered at the same dose rate.

In the only published report concerned with the effects of protons on primates, an RBE of 1.3 for mortality was reported for 730 Mev protons as compared to Co^{60} γ-radiation (20). Unfortunately, no evaluation of a possible dose-rate influence can be made because the proton dose rate was not given.

An experiment in which mice were irradiated with 138 Mev protons and Co^{60} γ-radiation showed that the 138 Mev proton to Co^{60} γ RBE was approximately 1 (18). In this study both types of radiation were given at 86, 256, and 550 rads/min. Therefore, if similar dose rates are used, the 138 Mev proton to 2 Mev x-ray RBE for primate mortality is most likely unity.

Unity RBE's for the hematologic studies were found. The changes in the hematologic measurements after 138 Mev proton irradiation followed patterns which were similar to those produced by 2 Mev x-rays and other electromagnetic radiations (2, 12, 13, 14). While the depression of the leukocyte counts, the platelet counts, and the hemoglobin-hematocrit levels in the present study was definitely the result of proton irradiation, the magnitude of these changes, however, was of little prognostic value. A similar situation was reported for primates irradiated with 2 Mev x-rays and for dogs irradiated with neutrons (actually mixed radiations-neutrons and γ-rays) (2, 21). While the neutrons certainly produced severe changes in the peripheral blood counts, the magnitude of the depression was of little value in predicting ultimate survival.

The suppression of bone marrow function as measured by Fe^{59} ferrokinetics also does not appear to be greatly different from the depression produced by x-rays and by radiations from a nuclear device (22, 23). The present results do show that doses as low as 210 rads of 138 Mev protons, while producing minimal mortality, definitely cause prominent changes in bone marrow function. Additional studies are under way in our laboratory in which bone marrow function is measured after relatively low doses (25 to 400 rads) of protons. These results will be included in a separate publication.

Experiments in which dogs were irradiated with neutrons produced results which are similar to the findings of the present study. The mortality after large doses of the neutrons tended to begin earlier than that caused by the standard electromagnetic radiation (21). Ainsworth et al. (24) related this occurrence, in part, to the depth dose distribution produced by their experimental arrangement. For the present study, however, this explanation would not be sufficient because the depth dose distribution was homogeneous for both the 138 Mev protons and the 2 Mev x-rays. The studies of Alpen et al. (21), in which the depth dose distribution was uniform, showed that the deaths

produced by neutron doses above the $LD_{50/30}$ levels occurred earlier than did the deaths caused by equivalent doses of 250 kvp x-rays.

The clinical courses of the dogs which had been irradiated with neutrons paralleled those of the proton-irradiated primates. In general, while these animals have had clinical findings similar to their x- or γ-irradiated counterpart, the severity of the gastrointestinal signs and the hemorrhagic diatheses has been more pronounced after exposure to the particulate radiation. The mortality patterns of proton- and neutron-irradiated mice indicate that these radiations produce relatively greater gastrointestinal injury than x- or γ-radiation (25-28).

No adequate explanation for the increased severity of the hemorrhagic diatheses after proton and neutron irradiation has been found. While one could make a tenuous case on the basis of a slightly more pronounced drop in platelet levels after 138 Mev protons as compared to equivalent doses of 2 Mev x-rays, this is not really satisfying because of the errors associated with performing platelet counts. The physical aspects of the proton irradiation of the bone marrow do not provide a satisfactory answer (29). If the marrow is considered to be encased by bone which is covered with soft tissue, the dose to the marrow would be slightly higher than if the bone density were replaced by unit-density soft tissue. Because of the relatively high density of bone, it will decrease the energy of the protons passing through it approximately 1.8 times greater than an equivalent thickness of soft tissue. Therefore, the protons traversing the marrow cavity will have a higher mass stopping power (LET) and will deliver a relatively larger dose. The biologic importance of this effect, however, seems negligible. If the bone thickness is 5 mm. (this would certainly be the thickest portion of the femur of the *Macaca mulatta*), the dose buildup would probably be less than 6%. Since most bone thicknesses are considerably smaller, the dose buildup would be proportionately reduced. The contribution of spallation products and other secondaries would be relatively minimal (10).

We must admit we do not know the mechanism responsible for the increased bleeding. The clinical findings, however, are certainly real. Every observer on our staff has commented at one time or another about the greater tendency toward hemorrhage in the proton-irradiated animals as compared with those that had been given Co^{60} γ-radiation or 2 Mev x-rays. The necropsies have provided similar evidence. Finally, we are left with merely reporting a clinical finding without being able to provide any insight as to mechanism.

In the primate, both LDH and SGOT levels are transiently elevated by 2 Mev x-rays and protons (2, 3). The patterns of the increases of the LDH concentrations are very similar for 138 Mev protons and 2 Mev x-rays. Therefore, the 138 Mev proton to Co^{60} γ RBE for changes in LDH concentrations should be considered to be unity. The possibility of increased synthesis, however, has not been excluded.

In conclusion, the results of this study have been shown that with respect to (1) mortality, (2) changes in the peripheral blood picture, (3) LDH and SGOT levels, and (4) necropsy findings, the 138 Mev protons and 2 Mev x-rays produce essentially identical findings. Differences in response produced by these two qualities of radiation are essentially clinical. Relatively more severe gastrointestinal signs and hemorrhage occur after proton irradiation as compared to the 2 Mev x-rays.

We consider the slight inhomogeneity of the proton field produced by the 1-cm. overlap of the exposure fields to have minimal significance. The amount of tissue which received the increased dose represents less than 5% of the total body volume. The region which was irradiated (the lower thorax and small portions of the upper areas) does not contain more than about 5% of the total body bone marrow. The irradiation of this small amount of marrow with a somewhat increased dose would be unlikely to influence the results to any great extent. Since the abdomen was not directly subject to this overdose of radiation, the exposure of a small volume of lung, muscle, and bone would not likely contribute to the clinical findings related to the gastrointestinal tract.

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Dalrymple, Glenn V., Captain, MC, USAF
Lindsay, Ian R., Wing Commander, RAF
Ghidoni, John J., Captain, MC, USAF
Mitchell, John C.
Kundel, Harold L., Captain, MC, USAF

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One hundred two primates (Macaca mulatta) were irradiated with spaced doses of 138 Mev protons ranging from 105 to 1,220 rads. An $LD_{50/30}$ of 516 ± 30 rads was estimated from the cumulative mortality data. A comparison of the proton $LD_{50/30}$ with the $LD_{50/30}$ from a previous study in which primates were irradiated with 2 Mev x-rays provides an estimate of 1.30 ± .09 (S.E.) for the mortality RBE. Adjusting the 2 Mev x-ray $LD_{50/30}$ to correspond to the 138 Mev proton dose rate gives an RBE of 1.04. Changes in total leukocyte count, lymphocyte count, neutrophil count, platelet count, hemoglobin concentration, hematocrits, LDH concentrations, and SGOT concentrations indicate an RBE of 1 for 138 Mev protons as compared to 2 Mev x-rays. The only findings which were significantly different between these qualities of radiation were clinical. Considerably more pronounced signs of gastrointestinal injury and hemorrhage were produced by 138 Mev protons as compared to equivalent doses of 2 Mev x-rays.

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